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REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
APPLICATION FOR A PATENT AND
ACKNOWLEDGEMENT OF RECEIPT
(Section 30(1) Regulation 22)

FORM P.1
(to be lodged in duplicate)

AS FILED

30 APR 1996

THE GRANT OF A PATENT IS HEREBY REQUESTED BY THE UNDERMENTIONED APPLICANT ON THE BASIS OF THE PRESENT APPLICATION FILED IN DUPLICATE

21	01	PATENT APPLICATION NO 96/3433

A&A REF 133208

71	FULL NAME(S) OF APPLICANT(S)

SCOTIA HOLDINGS PLC

ADDRESS(ES) OF APPLICANT(S)

EFAMOL HOUSE, WOODBRIDGE MEADOWS
GUILDFORD
SURREY GU1 1BA
ENGLAND

54	TITLE OF INVENTION

PRESENTATION OF BIOACTIVES

Only the items marked with an "X" in the blocks below are applicable.

[X] THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2. The earliest priority claimed is
Country: GB No: 9508823.3 Date: 1 MAY 1995

[ ] THE APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO 21 01

[ ] THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON
APPLICATION NO 21 01

THIS APPLICATION IS ACCOMPANIED BY:

- [X] XXXXXXXXXXXXXXXXXXr two copies of a complete specification of 40 pages
- [ ] Drawings of sheets
- [ ] Publication particulars and abstract (Form P.8 in duplicate) (for complete only)
- [ ] A copy of Figure of the drawings (if any) for the abstract (for complete only)
- [ ] An assignment of invention
- [ ] Certified priority document(s). (State quantity)
- [ ] Translation of the priority document(s)
- [ ] An assignment of priority rights
- [ ] A copy of Form P.2 and the specification of RSA Patent Application No 21 01
- [X] Form P.2 in duplicate
- [ ] A declaration and power of attorney on Form P.3
- [ ] Request for ante-dating on Form P.4
- [ ] Request for classification on Form P.9
- [ ] Request for delay of acceptance on Form P.4
- [ ] Extra copy of informal drawings (for complete only)

74	ADDRESS FOR SERVICE: Adams & Adams, Pretoria

DATED THIS 30TH DAY OF APRIL 1996

G.L. ERLANK

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

OFFICIAL DATE STAMP

REGISTRAR OF PATENTS

The duplicate will be returned to the applicant's address for service as proof of lodging but is not valid unless endorsed with official stamp

A&A P201

REPUBLIC OF SOUTH AFRICA

A & A Ref: 133208

ASSIGNMENT OF INVENTION

WHEREAS I/We (a) 1. DAVID FREDERICK HORROBIN 6. PETER REDDEN
2. MEHAR MANKU
3. AUSTIN MCMORDIE
4. PHILIP KNOWLES
5. ANDREA PITT

of (b) 1. SCOTIA HOUSE, CASTLE BUSINESS PARK, STIRLING, SCOTLAND K9 4TZ.
2-5. RESEARCH & DEVELOPMENT CENTRE, KINGSTOWN BROADWAY, KINGSTOWN INDUSTRIAL ESTATE, CARLISLE, CA3 0HA, ENGLAND.
6. UNIT 2, CHAPMAN DRIVE, ANNOPOLIS INDUSTRIAL ESTATE, P.O. BOX 818, KENTIVILLE, NOVA SCOTIA, CANADA, B4N 4H8.

am/are the inventor(s) of an invention entitled: (c) PRESENTATION OF BIOACTIVES

(hereinafter referred to as THE INVENTION)

AND WHEREAS (d) SCOTIA HOLDINGS PLC

(hereinafter referred to as THE ASSIGNEE(S) of (e) EFAMOL HOUSE, WOODBRIDGE MEADOWS
GUILFORD
SURREY GU1 1BA
ENGLAND

has/have for good and sufficient consideration agreed to acquire THE INVENTION from me/us in respect of THE REPUBLIC OF SOUTH AFRICA.

NOW THEREFORE I/We hereby assign THE INVENTION to THE ASSIGNEE(S) as far as the REPUBLIC OF SOUTH AFRICA is concerned, with the right to apply for Letters Patent his/their own name(s).

The assignment is made effective from the date of execution indicated below, or the date of filing of the application for THE INVENTION, or the date of execution of the Form P3 for THE INVENTION, whichever date is earliest.

DATED this (f) 6 day of June 1996

1) D Horrobin (g)

2) M S Manku

3) A McMordie

4) P. Knowles

5) A Pitt

6) Peter Redden

NOTE: No witness or legalization is necessary

ADAMS & ADAMS
Patent and Trade Mark Attorneys
PRETORIA

(a) Inventor's(s') full name(s).
(b) Inventor's(s') full address(es)
(c) Title of Invention.
(d) Assignee's(s') full name or names.
(e) Assignee's(s') address(es)
(f) Date of Execution.
(g) Signature(s) of Inventor(s).

A&A P101A

PRESENTATION OF BIOACTIVES

Field

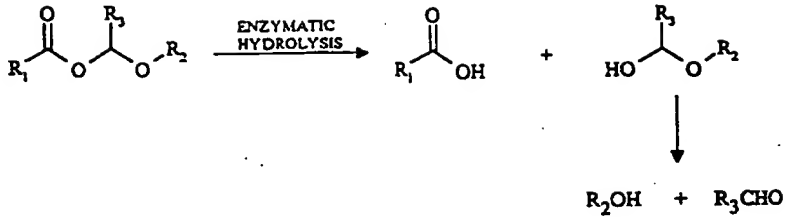
The specification relates to the presentation of bioactives, in which term we include a drug, essential nutrient or any other compound to be administered to the human or animal body in therapy or maintenance of health.

In particular, the specification relates to the presentation of such bioactives in a form in which they are lipophilic so that they can pass lipid barriers in the body readily, or to the presentation of two bioactives in the same molecule (where at least one of the bioactives is a fatty acid or fatty alcohol), or to the presentation of bioactives in a form which serves both aims and/or the aims of ready synthesis of such compounds without a chiral centre. From a drug regulatory viewpoint it is a great advantage to have two bioactives presented as a single molecule rather than as two separate entities. There may also be advantages in presenting known bioactives in novel ways. Those advantages include increased lipophilicity, the additive effects of two bioactives which are not normally presented together, and the sometimes synergistic effects of such bioactives.

The invention concerns the linking of bioactives (where at least one bioactive is an unsaturated fatty acid) through certain link molecules, specifically geminal dioxo and geminal amino oxo moieties considered in detail later herein, to yield geminal tripartate drugs, the synthesis of a range of compounds and their use in therapy and/or the maintenance of health.

Geminal Tripartate Mutual Prodrug Concept

Frequently simple ester mutual prodrugs of bioactives are not sufficiently labile *in vivo* to ensure a sufficiently high rate of conversion of the prodrug to the two desired bioactives. One reason is that for these simple ester mutual prodrugs the ester bond may be resistant to enzymatic attack for either steric or electronic reasons. One way to overcome this problem is to use the geminal tripartate mutual prodrug approach whereby the bioactives are linked via either a geminal dioxo or geminal amino oxo linkage. For



R_1 = Unsaturated Fatty Acid, R_2 = Bioactive, R_3 = H, Short Chain Alkyl Group

Scheme 2

Published Material

The concepts of linking unsaturated fatty acids to bioactives using the geminal dioxo or geminal amino oxo diester approach such as discussed above has received no great attention in the published patent and general literature with the exception of Terumo K.K. in EPA-0 222 155 which link 5-fluoro uracil to alpha linolenic acid, dihomo gamma linolenic acid, or eicosapentaenoic acid through a group -CH(R)-O- where R = methyl etc as, inter alia, anti-cancer agents.

Lipid Barriers

Many drugs act at the cell membrane surface by combining with cell surface receptors, or alternatively are taken into cells by specific transport systems. However, there are many drugs which, while they act within cells by modifying one of many different functions such as nucleic acid functions, the actions of intracellular enzymes, or the behaviour of systems like the lysosomes or the microtubules, are not able to penetrate cells effectively. There may be no receptors and transport systems with which they can link, or these systems may transport the drug into the cell at a less then optimum rate. Equally drugs may penetrate intracellular membranes such as mitochondrial and nuclear membranes at less than optimum rates.

There are other barriers to drug movements which are recognised as important. One of particular significance is the blood-brain barrier, which has many of the

2. Blood-brain barrier: all drugs acting on the central nervous systems will have their transport improved by this technique. This includes all drugs used in psychiatry, all drugs used in cerebral infections with any organism or in cerebral cancer and all other drugs acting on nerve cells such as anti-epileptic drugs and others acting on neurological disorders such as multiple sclerosis, amyotrophic lateral sclerosis, Huntington's chorea and others.

3. Skin: as with the blood-brain barrier, all drugs that may be required to penetrate the skin to achieve a systemic effect will benefit from their conversion to a fatty acid derivative.

For example, the approach discussed is applicable to amino acids. Of particular interest are those which seem to play roles in the regulation of cell function as well as acting as components of proteins. Examples include tryptophan (a precursor of 5-hydroxytryptamine [5-HT], a key regular of nerve and muscle function), phenylalanine (a precursor of catecholamines) and arginine (a regulator of the synthesis of nitric oxide which also plays important roles in controlling cellular activities).

Properties Conferred Generally

Generally the compounds proposed herein have many advantages in addition to their lipophilicity. Two moieties of a given fatty acid or even a single moiety may be delivered, in a form which is readily incorporated into the body as an oral, parenteral or topical formation; which is very well tolerated with none of the side effects associated, for example, with free fatty acids; which is not too stable to be properly utilised.

When two different fatty acids are to be delivered, the advantages are as before plus the ability to administer simultaneously two materials with different biological actions in a single molecule. This avoids the regulatory problems which ensue when two materials are administered as separate compounds. When two drugs are delivered as separate molecules, regulatory authorities normally require each drug to be studied alone

corresponding fatty alcohol. Conjugated linoleic and columbinic acids are examples of fatty acids which in themselves have valuable properties and are likely to be of particular use. References to fatty acids are accordingly to be read herein as to both forms, except where the chemistry of one or the other specifically is under discussion. The desirable properties of GLA and DGLA however, make them especially valuable for the purpose.

The essential fatty acids, which in nature are of the all - cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g. z,z-octadeca - 9,12 - dienoic acid or z,z,z,z,z,z-docosa-4,7,10,13,16,19 - hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2n-6 or 22:6n-3 are convenient. Initials, e.g., EPA and shortened forms of the name e.g. eicosapentaenoic acid are used as trivial names in some of the cases.

FIGURE 1

n-6 EFA's		**n-3 EFA's**
18:2n-6 (Linoleic acid, LA)		18:3n-3 (α-Linolenic acid, ALA)
↓	δ-6-desaturase	↓
18:3n-6 (γ-Linolenic acid, GLA)		18:4n-3 (Stearidonic acid, SA)
↓	elongation	↓
20:3n-6 (Dihomo-γ-linolenic acid, DGLA)		20:4n-3
↓	δ-5-desaturase	↓
20:4n-6 (Arachidonic acid, AA)		20:5n-6 (Eicosapentaenoic acid, EPA)
↓	elongation	↓
22:4n-6 (Adrenic acid)		22:5n-3
↓	δ-4-desaturase	↓
22:5n-6		22:6n-3 (Docosahexaenoic acid, DHA)

c) Amino acids

d) Vitamins particularly of the B group, and other essential nutrients.

e) Cytokines and peptides

f) Neurotransmitters and neurotransmitter precursors.

g) Phospholipid head groups such as inositol, choline, serine and ethanolamine, which may be linked directly or via the phosphate moiety.

h) Aromatic fatty acids such as phenylacetic acid, phenyl butyric acid and cinnamic acid which are of particular value in cancer treatment.

Efficacy

The combination of the therapeutic effect of a drug with the therapeutic effect of a fatty acid may be considered through examples:-

a) Psychotropic drugs may be linked to fatty acids such as GLA, DGLA, arachidonic acid, eicosapentaenoic acid or docosahexaenoic acid which have important roles in brain function, so providing a dual therapeutic effect.

b) Drugs used for the treatment of cardiovascular disease may be attached to a fatty acid which also has value in such treatment, such as eicosapentaenoic acid which lowers triglyceride levels and inhibits platelet aggregation, or GLA or DGLA which lower cholesterol levels and have vasodilator action, or arachidonic acid which is a potent cholesterol lowering agent, or DHA which has anti-arrhythmic properties.

c) Drugs used in the treatment of any form of inflammation may be linked to a fatty acid such as gammalinolenic acid, dihomo-gammalinolenic acid or eicosapentaenoic acid or docosahexaenoic acid which also has anti-inflammatory action.

d) Drugs used in the management of osteoporosis may be linked to GLA or DGLA which enhance the incorporation of calcium into bone, or to EPA or DHA which reduces urinary calcium excretion.

would do the rest. It is now widely accepted that this is not true. Different diseases may have different abnormal patterns of EFAs and because of problems in metabolism these cannot simply be corrected by giving linoleic or alpha-linolenic acid. It is therefore appropriate in many situations to provide increased amounts of one of the other EFAs or to give two or more of the EFAs simultaneously. While the EFAs can be supplied in various forms and in various mixtures, it is convenient in both nutrition and in medical treatment to be able to supply the fatty acids as particular molecules. Equally in various situations it may be desirable to give the EFA or other fatty acid in association with an amino acid, vitamin, drug or other molecule which in itself has desirable properties.

To date, proposals for administration of two fatty acids simultaneously have been in terms of particular triglycerides, following the natural occurrence of essential fatty acids in triglyceride form. However, triglycerides, unless symmetrical about the 2-carbon, are chiral and that fact, coupled with acyl migration between the alpha and beta positions makes the synthesis of specific triglycerides a difficult task. Such migration may take place after synthesis creating particular problems in a drug regulatory context. The lack of specificity when two fatty acids are present in the same triglyceride molecule creates many problems in synthesis, pharmacology, formulation and stability. Moreover triglycerides can be slow and difficult to synthesise.

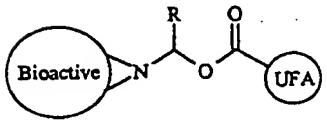
For purposes of convenient administration of different fatty acids simultaneously or indeed of a single fatty acid in high amounts in well tolerated form, use can be made of the geminal tripartate mutual prodrug approach discussed earlier herein, and in detail later.

Chemical Nature of Bioactives which may be derivatised according to the present disclosure

The present specification covers tripartate prodrugs in which unsaturated fatty acids and unsaturated fatty alcohols are linked to bioactives with an available carboxyl, alcohol, or acidic NH group through a geminal dioxo or geminal amino oxo linkage as appropriate.

(c) bioactives with an acidic NH group (these include amides, imides, hydantoins, tertiary or N-heterocyclic amines and generally other NH acidic compounds)- these may be derivatives as follows:

amino/ester coupling with unsaturated fatty acid via geminal amino oxo linkage



In all of these categories "unsaturated fatty acid" (and the derived "unsaturated fatty alcohol") represents a member of a group comprising oleic acid (and oleoyl alcohol) and any fatty acid (or corresponding fatty alcohol) with two or more *cis* or *trans* double bonds. However, the fatty acids likely to be of most value in this context are the essential fatty acids shown in fig. 1 and in particular GLA, DGLA, AA, SA, EPA and DHA. For particular purposes conjugated linoleic acid and columbinic acid may be of great interest.

In all of these categories, R is either H, fully hydrocarbon in nature or containing heteroatoms (including ring substituted aromatics) corresponding with these definitions.

Represents the fatty acid alkyl chain corresponding with these definitions

General Discussion of Synthesis

The individual fatty acids may be purified from natural animal, vegetable or microbial sources or may be chemically synthesised by methods known to those skilled in the art or developed hereafter.

(e) by reaction of an α-halogenated alkyl ester with an alcohol in the presence of a suitable organic tertiary base, e.g. triethylamine, or suitable inorganic base, e.g. potassium carbonate, in a suitable inert solvent, e.g. dimethylformamide, at a temperature between 0°C and 120°C under an inert atmosphere.

(f) by reaction of an α-halogenated alkyl ether with an acid in the presence of a suitable organic tertiary base, e.g. triethylamine, or suitable inorganic base, e.g. potassium carbonate, in a suitable inert solvent, e.g. dimethylformamide, at a temperature between 0°C and 120°C under an inert atmosphere.

Derivatisation of bioactives in class (c) may be prepared by any reasonable synthesis of amino/ester linked by a geminal amino oxo group and especially:

(g) by reaction of an α-halogenated alkyl ester with an acidic NH compound in the presence of a suitable organic tertiary base, e.g. triethylamine, or suitable inorganic base, e.g. potassium carbonate, in a suitable inert solvent, e.g. dimethylformamide, at a temperature between 0°C and 120°C under an inert atmosphere.

(h) by reaction of an N-hydroxyalkylated compound with acid chloride, acid anhydride or suitably activated ester with or without the presence of an organic tertiary base, e.g. pyridine, in a suitable inert solvent, e.g. dichloromethane, at a temperature between 0°C and 120°C.

(i) by reaction of an N-hydroxyalkylated compound with acid in the presence of a condensing agent, e.g. 1,3-dicyclohexylcarbodiimide, with or without the presence of a suitable organic tertiary base, e.g. 4-(N,N-dimethylaminopyridine), in an inert solvent, e.g. dichloromethane, at a temperature between 0°C and 50°C.

(j) by reaction of alcohol with acid or acid, short or medium chain alkyl ester, or acid, activated ester, e.g. vinyl, in the presence of a hydrolase enzyme, e.g. hog liver esterase, with or without a suitable solvent, e.g. hexane, at temperatures between 20° and 80°C under conditions such that the water or alcohol or aldehyde byproduct is removed, e.g. under vacuum.

Aromatic acids

GLA-phenylbutyric acid, GLA-phenylacetic acid, GLA-trans-cinnamic acid and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any aryl alkanoic or aryl alkenoic acid.

Steroids

GLA-hydrocortisone, GLA-oestradiol, GLA- and DHA-dehydroepiandrosterone and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any natural or synthetic steroid, such as any oestrogen, any progestin, any adrenal steroid and any anti-inflammatory steroid, particularly betamethasone, prednisone, prednisolone, triamcinolone, budesonide, clobetasol, beclomethasone and other related steroids.

Anti-oxidants

GLA-lipoic acid, DHA-lipoic acid, GLA-tocopherol, di-GLA-3,3'-thiodipropionic acid and in general any of e.g. GLA, DGLA, AA, SA, EPA or DHA with any natural or synthetic anti-oxidant with which they can be chemically linked. These include phenolic anti-oxidants (e.g. eugenol, carnosic acid, caffeic acid, BHT, gallic acid, tocopherols, tocotrienols and flavonoid anti-oxidants (e.g. myricetin, fisetin)), polyenes (e.g. retinoic acid), unsaturated sterols (e.g. Δ^5-avenosterol), organosulfur compunds (e.g. allicin), terpenes (e.g. geraniol, abietic acid) and amino acid antioxidants (e.g. cysteine, carnosine).

Drugs

GLA and indomethacin, ibuprofen, fluoxetine, ampicillin, penicillin V, sulindac, salicylic acid, metronidazole, fluphenazine, dapsone, tranylcypromine, acetyl carnitine, haloperidol, mepacrine, chloroquine, penicillin, tetracycyline, pravastatin, bisphosphonates such as efidronic acid, pamidronic acid and clordronic acid and their sodium salts, adenosylosuccinate and adenylosuccinate and related compounds and agents used as x-ray contrast media, and in general any of e.g. GLA, DGLA, AA, SA, EPA or

undisclosed and particularly significant. Indeed it offers a favourable way to give a singly fatty acid as the geminal dioxo diester. Further, apart from administering individual acids, such geminal dioxo diesters may have value in pharmaceutical formulation as emulsifiers.

The UFA geminal dioxo diesters have a wide variety of possible uses. They may be used as pharmaceuticals for the treatment or prevention of diseases in which abnormalities of fatty acids have been identified. They may be added to foods or added to or used as nutritional supplements for those who require the particular fatty acid for the treatment or prevention of diseases. They may also be used in foods or pharmaceuticals for veterinary use. They may further be used for skin care.

As advantages or in various particular aspects the invention provides:

(i) A convenient and safe way of administering, for therapeutic or nutritional purposes, one or two unsaturated fatty acid moieties, or one unsaturated fatty acid and one bioactive that is not a fatty acid.

(ii) A derivative, of a bioactive required to cross lipid membranes in the body to exert its action whether in entry to a cell or in passing the skin, blood-brain or other barrier, through a geminal dioxo or geminal amino oxo linkage to an essential fatty acid of the natural n-6 or n-3 series and especially GLA or DGLA, AA, SA, EPA or DHA or the related fatty acids cLA or CA.

(iii) A fatty acid derivative of a drug such that the drug and fatty acid are mutually efficacious.

(iv) A method of improving the transport of a drug across lipid membranes in the body, characterised by the administration of the drug in a form as above.

(v) A method of manufacture of a medicament for improved therapy involving transport of a drug across lipid membranes in the body, characterised by incorporating the drug in a medicament in a form as above.

(vi) A method of manufacture of a medicament for delivering one or two fatty acids from the list in (ii) above or for delivering one of those fatty acids in association with another active agent.

5. Improvements in calcium balance with increased calcium absorption, reduced calcium excretion, increased deposition of calcium in bones and reduced ectopic deposition of calcium in tissues such as arteries and kidneys.

6. Anticancer effects of three sorts, selective cytotoxic damage and induction of apoptosis in cancer cells but not in normal cells, inhibition of growth by reduction of action of growth factors and interference with second messenger systems required for growth, inhibition of metastasis by various actions including increased expression of E-cadherins and inhibition of proteolytic enzymes such as urokinases, lipoxygenase and matrix metalloproteinases, and inhibition of cancer-associated cachexia.

7. Actions on nerve cells including maintenance of normal nerve membrane structure and function and the normal pre- and post-synaptic actions of neurotransmitters.

These desirable actions mean that this group of fatty acids can be used in the treatment of may different disorders including cardiovascular disorders of many types, inflammatory disorders including rheumatoid arthritis, osteoarthritis, ulcerative colitis and Crohn's disease, respiratory disorders including asthma, psychiatric disorders including schizophrenia, alcoholism, attention deficit disorder, depression and Alzheimer's disease, neurological disorders including multiple sclerosis and Huntington's chorea, renal and urinary tract disorders including various types of renal inflammatory disease and urinary calcium stones, metabolic disorders including osteoporosis and ectopic calcification, and gastrointestinal ulcerative and inflammatory diseases. Although conjugated linoleic acid (cLA) has not been nearly as widely tested as, say GLA or EPA, it also seems to have a wide range of actions including effects valuable in the treatment of cancer, cardiovascular and metabolic diseases.

GLA, DGLA, AA and columbinic acid have desirable actions on the skin and are particularly valuable in the treatment of skin diseases such as atopic eczema, psoriasis, urticaria and allergic reactions.

remarkably non-toxic and can be administered safely in large doses without the risk of important side effects.

Specific uses of compounds containing geminal dioxo or geminal amino oxo linkage(s)

1. Geminal dioxo or geminal amino oxo moiety-containing compounds containing: two fatty acids in which one fatty acid is GLA or DGLA and the other is GLA, DGLA, SA, EPA, DHA, cLA (conjugated linoleic acid) or CA (columbinic acid) for the treatment of:-

(a) complications of diabetes, particularly neuropathy and retinopathy; and improvement of responses to insulin in diabetes and pre-diabetes;

(b) cancers;

(c) osteoarthritis;

(d) rheumatoid arthritis;

(e) other inflammatory and auto-immune diseases including Sjogren's syndrome, systemic lupus, ulcerative colitis, Crohn's disease and uveitis;

(f) respiratory diseases including asthma;

(g) neurological disorders including multiple sclerosis, Parkinson's disease and Huntington's chorea;

(h) renal and urinary tract disorders;

(i) cardiovascular disorders;

(j) degenerative diseases of the eye including retinitis pigmentosa and senile macular degeneration;

(k) psychiatric disorders including schizophrenia, Alzheimer's disease, attention deficit disorder, alcoholism and depression;

(l) prostatic hypertrophy and prostatitis;

(m) impotence and male infertility;

(n) mastalgia;

(o) male pattern baldness;

(d) carnitine or carnitine derivatives for the treatment of any disease but especially muscle weakness, cardiac failure, chronic fatigue syndrome, Alzheimer's disease, and peripheral neuropathies;

(e) any other amino acid or related substance for the treatment of any disease or aminolevulinic acid or derivative thereof for the treatment of any disease but especially cancers;

(f) adenylosuccinate or related substances for the treatment of any disease but especially muscular dystrophy, cardiac failure, chronic fatigue and Alzheimer's disease and other dementias;

(g) aspirin, salicylic acid, indomethacin, ibuprofen, or any other non-steroidal anti-inflammatory drug for the treatment of any disease but especially of inflammatory disorders of pain, of Alzheimer's disease and other dementias and of any disease in which platelet aggregation should be inhibited;

(h) any antibiotic for the treatment of any appropriate infectious disease but especially tetracycline, clindamycin, minocycline, chlortetracycline and erythromycin for the treatment of acne;

(i) any anti malarial or anti-protozoal drug for the treatment of any disease, but especially chloroquine, mepacrine, quinacrine and mefloquine for the treatment of malaria, protozoal disorders, inflammatory disorders and schizophrenia;

(j) any antifungal drug for the treatment of any disease but especially metronidazole and antifungal imidazoles and nitroimidazoles and amphotericin for the treatment of fungal infections of various types;

(k) any anti-inflammatory steroid for the treatment of any disease but especially hydrocortisone and betamethasone for the treatment of skin disorders and beclomethasone and budesonide for the treatment of asthma.

(l) any gonadal steroid for the treatment of any disease but especially oestrogens and progestogens for the treatment of ovarian deficiency and osteoporosis and androgens for the treatment of testicular deficiency;

(y) any antiepileptic drug used for any disease, but especially phenytoin, carbamazepine, valproate, ethosuximide, vigabatrin or lamotrigine for the treatment of epilepsy;

(z) any hypolipidaemic agent for the treatment of any disease but especially fibrates and statins used for cholesterol lowering and cholesterol modification;

(aa) any oral hypoglycaemic or insulin-sensitising agents used in the management of diabetes;

(bb) any bisphosphonates used in the management of osteoporosis, Paget's disease or cancer;

(cc) any contrast agents used in radiology including diatrizoate compounds, iodipamide, ioglycamates, iopanoates, iophendylate, iothalamate, ioxaglate, metrizamide and related compounds;

(dd) any peptide or protein for use in the treatment of diseases for which the peptide or protein itself is used, including insulin, calcitonin, erythropoietin and other peptides;

(ee) any vitamin used in the treatment of any disease, or used in foods, nutritional supplements or food additives as a way of providing the vitamin effectively;

(ff) any antioxidant used in the management of any disease, but especially for those diseases in which antioxidants may be especially beneficial including cardiovascular diseases, cancer and inflammatory disorders and any antioxidant used as a food or other preservative or as a component of a food, food additive or nutritional supplement;

(gg) any porphyrin, chlorin or bacteriochlorin-based drug especially tetrakis(hydroxyphenyl) derivatives thereof used in photodynamic therapy of cancers.

Formulations

The fatty acid-bioactive geminal dioxo and amino oxo conjugates may be formulated in any way appropriate and which is known to those skilled in the art of

Part 2: α-(z,z,z-octadeca-6,9,12-trienoyloxy)-methyl-z,z,z-octadeca-6,9,12-trienoate.

To a solution of z,z,z-octadeca-6,9,12-trienoic acid (85 mg) in 400 µl of dry pyridine with stirring in an atmosphere of nitrogen was added α-chloromethyl z,z,z-octadeca-6,9,12-trienoate (100 mg) and triethylamine (43 µl). The mixture was heated at 80°C for 5 hours after which tlc indicated the reaction had gone to completion. The pyridine was evaporated and the residue dissolved in chloroform, washed with water, dried, concentrated and purified by flash column chromatography to give α-(z,z,z-octadeca-6,9,12-trienoyloxy)-methyl-z,z,z-octadeca-6,9,12-trienoate as a clear oil.

Example 2

α-(z,z,z-octadeca-6,9,12-trienoyloxy)-methyl-z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoate

(Geminal dioxo diester of GLA with EPA)

To a solution of z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoic acid (104 mg) in 400 µl of dry pyridine with stirring in an atmosphere of nitrogen were added α-chloromethyl z,z,z-octadeca-6,9,12-trienoate (113 mg) and triethylamine (48 µl). The mixture was heated at 80°C for 5 hours after which tlc indicated reaction had gone to completion. The pyridine was evaporated and the residue dissolved in chloroform and washed with water, dried, concentrated and purified by flash column chromatography to give α-(z,z,z-octadeca-6,9,12-trienoyloxy)-methyl-z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoate as a clear oil.

Example 3

α-(z,z,z-octadeca-6,9,12-trienoyloxy)-methyl-1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate

(Geminal dioxo diester of GLA with indomethacin)

1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (108 mg), α-chloromethyl z,z,z-octadeca-6,9,12-trienoate (100 mg) and triethylamine (47 µl) were

(±)-α-(z,z,z-octadeca-6,9,12-trienoyloxy-α-methyl)-methyl-2,3,5-triiodobenzoate

(Geminal dioxo diester GLA with triiodobenzoic acid)

Part 1: (±)-α-chloroethyl z,z,z-octadeca-6,9,12-trienoate

Anhydrous zinc chloride (300 mg) was added to z,z,z-octadeca-6,9,12-trienoyl chloride (35.6g). Acetaldehyde (5.2g) was added dropwise with stirring over 30 minutes in an ice bath under an atmosphere of nitrogen. The reaction mixture was then stirred at room temperature for an additional 40 minutes and was shown to be complete by tlc. Water was added and the mixture was extracted twice with diethyl ether. After drying the solvent was evaporated to give (±)-α-chloroethyl z,z,z-octadeca-6,9,12-trienoate as a clear oil.

Part 2: (±)-α-(z,z,z-octadeca-6,9,12-trienoyloxy-α-methyl)-methyl-2,3,5-triiodobenzoate

To a solution of 2,3,5-triiodobenzoic acid (220 mg) in 400 µl of dry pyridine and 200 µl of DMF with stirring in an atmosphere of nitrogen was added (±)-α-chloroethyl z,z,z-octadeca-6,9,12-trienoate (150 mg) and triethylamine (61 µl). The mixture was heated at 80°C for 2.5 hours after which tlc indicated the reaction had gone to completion. The organic solvents were evaporated and the residue dissolved in chloroform, washed with water, dried, concentrated and purified by flash column chromatography to give (±)-α-(z,z,z-octadeca-6,9,12-trienoyloxy-α-methyl)-methyl-2,3,5-triiodobenzoate as a clear oil.

Example 7

(±)α-(z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoyloxy-α-methyl)-methyl-1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate

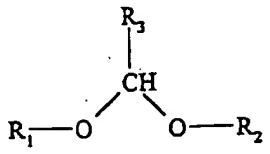
(Geminal dioxo diester of EPA with indomethacin)

Part 1: (±)-α-chloroethyl z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoate

z,z,z,z,z-Eicosa-5,8,11,14,17-pentaenoyl chloride (7g), zinc chloride (51 mg) and acetaldehyde (0.92g) were reacted together and purified as described in Example 6, Part 1 to give (±)-α-chloroethyl z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoate as a clear oil.

CLAIMS

1. Compounds of the following structure, and when for use in therapy:-



where R_1 is an acyl group derived from a C_{16-30} fatty acid with two or more *cis* or *trans* double bonds and particularly an n-6 or n-3 series EFA or conjugated linoleic acid, or columbinic acid, or parinaric acid and R_2 is as R_1 the same or different, or any other nutrient, drug or other bioactive residue released as the active in the body and R_3 is either hydrogen, fully hydrocarbon, or containing heteroatoms, preferably an alkyl group particularly a C_1-C_4 alkyl group.

2. A compound according to claim 1, wherein the fatty acid is gamma-linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid, adrenic acid, stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid n-3 or docosahexaenoic acid.

3. A compound according to claim 1 or 2 where R_2 is a drug or other active required to cross lipid membranes in the body to exert its action whether in entry to or movement within a cell in which it is to act, or in passing the skin, blood-brain or other barrier.

4. A compound according to claim 1 or 2, wherein R_2 is a drug, vitamin, amino acid, anti-oxidant or other active which is required to have an action additive to, complementary to, or synergistic with R_1.

(q) dermatological disorders, including atopic eczema, hand eczema, psoriasis, urticaria and allergic disorders;

(r) dyslexia and other learning disabilities;

(s) cancer cachexia.

7. Compounds according to claim 1 containing two fatty acids in which one fatty acid is AA and the other is AA, GLA, DHA, DGLA or EPA for treatment of the disorders set out in claim 6 and especially (a), (g), (i), (j), (k), (q) and (r).

8. Compounds according to claim 1 containing two fatty acids in which one fatty acid is EPA and the other is EPA or DHA for the treatment of any of the disorders set out in claim 6 but especially (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (p), (r) and (s).

9. Compounds as set out in claims 6 to 8 used as a component of a food, particularly of a functional food or nutraceutical for the promotion of health, as a nutritional supplement or as a food additive.

10. Compounds as set out in claims 6 to 8 used for enteral or parenteral administration in products used in clinical nutrition.

11. Compounds as set out in claims 6 to 8 used as a component of a cosmetic or other preparation used in the care of the skin or the hair.

12. Compounds according to claim 1 in which one position is occupied by a fatty acid drawn from GLA, DGLA, AA, SA, cLA, EPA or DHA and the other position is occupied by an agent, selected from the following list, whose chemical structure is such that it can be linked by one of the linkages described herein:

(j) any antifungal drug for the treatment of any disease but especially metronidazole and antifungal imidazoles and nitroimidazoles and amphotericin for the treatment of fungal infections of various types;

(k) any anti-inflammatory steroid for the treatment of any disease but especially hydrocortisone and betamethasone for the treatment of skin disorders and beclomethasone and budesonide for the treatment of asthma.

(l) any gonadal steroid for the treatment of any disease but especially oestrogens and progestogens for the treatment of ovarian deficiency and osteoporosis and androgens for the treatment of testicular deficiency;

(m) any adrenal steroid for the treatment of any disease, but especially dehydroepiandrosterone for the treatment of disorders associated with ageing;

(n) any retinoid for the treatment of any disease but especially tretinoin and isotretinoin for the treatment of dermatological disorders and for use in skin care;

(o) any anticancer agent for the treatment of cancer;

(p) any antipsychotic agent for the treatment of schizophrenia and other psychoses;

(q) any antidepressive agent for the treatment of any disease but especially for the treatment of depression;

(r) any anti-anxiety agent for the treatment of any disease, but especially for the treatment of anxiety and panic attacks;

(s) any immunosuppressive agent for the treatment of any disease but especially cyclosporine and tacrolimus for the control of immunity after organ transplantation and for the treatment of autoimmune and inflammatory disorders including psoriasis, eczema, asthma, rheumatoid arthritis and inflammatory bowel disease;

(t) any proton pump inhibitor or H2 antagonist for the treatment of any disease but especially diseases associated with excess gastric acid production or reduced defences against gastric acidity;

used as a food or other preservative or as a component of a food, food additive or nutritional supplement;

(gg) any porphyrin, chlorin or bacteriochlorin-based drug especially tetrakis(hydroxyphenyl) derivatives thereof used in photodynamic therapy of cancers.

13. Use of a compound according to claim 1 containing two fatty acids in which one fatty acid is GLA or DGLA and the other is GLA, DGLA, SA, EPA, DHA, cLA (conjugated linoleic acid) or CA (columbinic acid) in the manufacture of a medicament to treat a disease, disorder or condition set out in claim 6.

14. A compound as claimed in claim 1, substantially as herein described and illustrated.

15. A method as claimed in claim 5, substantially as herein described and illustrated.

16. A compound for the treatment of a disease, disorder or condition, substantially as herein described and illustrated.

17. Use as claimed in claim 13, substantially as herein described and illustrated.

18. A new compound, substantially as herein described.

19. A new non-therapeutic method of treatment, substantially as herein described.

20. A substance or composition for a new use in a method of treatment, substantially as herein described.

21. New use of a compound according to claim 1, substantially as herein described.

DATED THIS 30TH DAY OF APRIL 1996

[redacted] ERLANK

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS